



# Out-of-pocket costs analysis of ifosfamide, epirubicin, and etoposide (IEV) and etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin (ESHAP) regimens in the patients with relapsed and refractory lymphoma in Iran

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## Original Article

### Abstract

**BACKGROUND:** This is an out-of-pocket costs analysis of ifosfamide, epirubicin, and etoposide (IEV) and etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin (ESHAP) drug regimens in treatment of lymphoma in Iran.

**METHODS:** This cross-sectional study was conducted in Shiraz City. Data were collected using a data-collection form. The social perspective was used to collect cost data. Three types of costs were measured, medical direct costs, non-medical direct costs, and indirect costs.

**RESULTS:** 65 patients were treated with these two methods; 27 patients were treated with IEV and 38 with ESHAP. Moreover, the mean direct cost in IEV and ESHAP regimens in 2014 were  $1191.10 \pm 610.74$  and  $1819.57 \pm 789.73$  United States dollars (USD), respectively. The difference was statistically significant ( $P < 0.001$ ).

**CONCLUSION:** In this study, costs in the IEV regimen were significantly lower than the ESHAP regimen. This was particularly caused by an earlier discharge of patients under IEV regimen; since these patients experienced a trend toward less neutropenia and, hence, had a trend toward fewer hospitalization days, the related cost was 3451.76 USD with savings of 6479.61 USD compared with the ESHAP regimen. Overall, most of patient's income was spent on out-of-pocket costs for all expenditures incurred because of lymphoma.

**KEYWORDS:** Lymphoma, Cost, IEV Protocol, ESHAP Protocol

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## Introduction

The number of patients with cancer will increase to 24 million in the world by 2035.<sup>1</sup> In 2018, in the United States, there will be an estimated 1,050 deaths from Hodgkin lymphoma (HL), and 19,910 deaths from non-Hodgkin lymphoma (NHL). From 2006 to

2015, death rates decreased by about 3% per year for Hodgkin lymphoma, and 2% per year for non-Hodgkin lymphoma.<sup>2</sup>

The National Institutes of Health (NIH) estimates that the overall costs of cancer contains medical direct costs, non-medical direct costs, and indirect costs; in 2009, in the United States, the costs were totally 216,000,000,000 United States dollars (USD), 86,000,000,000 USD caused by direct costs, and 130,000,000,000 USD by indirect costs.<sup>3</sup> It determined that the associated

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direct costs of cancer care would increase by 27%, assuming stable incidence, survival, and costs; if cost of care increased each year by 2%, in the first year after diagnosis and in the last year of life, the predicted 2020 cost would increase up to 39% from 2010.<sup>4</sup>

After primary treatment for Hodgkin and non-Hodgkin lymphomas, 10 to 20 percent of the patients with early-stage disease, and 35 to 40 percent of patients with advanced stage at diagnosis will suffer a relapse.<sup>5,6</sup> Patients who are refractory to the first-line therapy or relapse at a later stages, need more care.<sup>7</sup> Roughly, 50 to 60 percent of patients who relapse may be successfully treated with high-dose chemotherapy and stem-cell transplantation.<sup>7,8</sup> Patients with lymphoma are usually treated with chemotherapy; radiation, alone or in composition with chemotherapy, is used less usually.<sup>9</sup> Typically, chemotherapy for lymphoma is a therapeutic protocol or pharmaceutical regimen that includes several drugs. Etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin (ESHAP) is a drug regimen,<sup>7</sup> which is effective in treating refractory or relapsed lymphoma.<sup>10</sup> In addition, ifosfamide, epirubicin, and etoposide (IEV) is a combination of ifosfamide, epirubicin, and etoposide.<sup>11</sup>

These drug regimens have different effects on costs. Because of the various medical costs in cancer treatment, and maybe the impact on total treatment costs, and also the limited information about the costs, we performed a study to analysis the costs of IEV versus ESHAP, which are commonly used treatments for treating these patients in Iran.

## Materials and Methods

This cross-sectional study was conducted as a double-blind study on 65 patients suffering from relapsed/refractory lymphoma, in Amir Oncology Hospital in Shiraz City, Iran. Patients were selected from April 2013 to April 2014, using goal-oriented sampling. The

geographic area of study was the urban and rural areas of Fars Province.

We used telephone interviews for measuring the costs for household members resulted from lymphoma. The data collection form was completed during the interview after 6 months of follow-up at the last (6<sup>th</sup>) session of chemotherapy for each patient. Information on type of treatment regimens and drug effects was obtained through review of medical records. All participants provided signed informed consent. All the ethics review committees of participating hospital approved the study.

All node-positive patients younger than 75 years were included. Patients with severe renal failures, hepatic impairments, Karnofsky Performance Scale Index of less than 70, and age older than 75 years, and all the cases of metastasis and node negative were excluded.

The social perspective was used to collect cost data for a period of 6 months. Moreover, the data collection form was used to collect demographic data and costs. We defined out-of-pocket costs as all costs amounts paid directly by the patients due to relapsed/refractory lymphoma cancer treatment. For patients, out-of-pocket costs included costs associated with medical direct cost (medication, hospitalization, sonography, radiology, magnetic resonance imaging (MRI), surgical costs, laboratory tests, computed tomography (CT) scan, and follow-up visits), non-medical direct costs (travel costs, lodging, phone, auxiliary equipment, and special diet during chemotherapy), and indirect costs (costs of lost production due to absence from work) calculated using the Human Capital Approach. Out-of-pocket costs were calculated by summing these items. We also questioned patients about their perceptions of the family's financial situation in the past 6 months, using questions administered at the 1-month interviews. These questions were adapted from published studies and questionnaires.<sup>12</sup>

Specifically, we asked about the patient's satisfaction with their family's financial situation, and their worry about and perception of their family's financial situation compared with that of others of the same age. For these analyses, patients not working at diagnosis were assigned 0 USD in terms of the indirect costs. The total of these items were treatment costs for each patient, calculated by the Iranian Rial (IRR) to USD exchange rate in year 2014.

In order to estimate transmission costs for those who travelled with their personal car, we used the dimension between the patient's domicile and the treatment hospital. We asked the cost of petrol from patients or patients accompany. The resulting amount was multiplied by two to account for the return trip, and then multiplied by the number of treatments received. We used the paid amount for those travelling by taxi, bus, rail, and air. None of the respondents reported having paid for parking. For those living away from home, we calculated lodging costs by using the cost for lodging reported by the respondent, and 0 USD for respondents who stayed in family or friends' home. The phone costs, auxiliary equipment, and special diet were estimated using the paid amount by the patients multiplied by the number of those. In addition, we estimated extra out-of-pocket costs incurred because of patients with relapsed/refractory lymphoma for indoor and outdoor household help, and child care.

We used descriptive statistical to analyze the data via SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). Moreover, the Mann-Whitney test was used to assess the significant differences in costs between the two regimens. Besides, 95% of confidence intervals (CIs) were computed using non-parametric bootstrapping method for costs.

## Results

According to table 1, in IEV and ESHAP regimens, the highest and lowest mean costs were medical direct costs ( $1191.10 \pm 610.74$  USD in IEV and  $1819.57 \pm 789.73$  USD in ESHAP) and non-medical direct costs ( $237.06 \pm 207.42$  USD in IEV and  $208.39 \pm 179.7$  USD in ESHAP), respectively. Moreover, the mean medical direct costs was statistically lower in IEV regimen than ESHAP regimen ( $P < 0.001$ ). But, for the mean of non-medical direct costs and indirect costs and total costs, the differences were not statistically significant.

As seen in table 2, the total cost of chemotherapy drugs in the IEV regimen was 13201.45 USD ( $488.94 \pm 338.57$  USD) that was highest medical direct costs. Moreover, in the ESHAP regimen, this item was 32943.08 USD ( $866.92 \pm 354.91$  USD). In both regimens, travel costs and indirect costs were highest type of treatment costs, in IEV regimen, 4037.14 ( $149.52 \pm 142.95$ ) and 16152.60 ( $562.2 \pm 584.25$ ) USD, and in ESHAP regimen, 3980.62 ( $104.75 \pm 98.56$ ) and 17,359.7 ( $351.65 \pm 666.09$ ) USD, respectively.

**Table 1. The treatment costs of patients with lymphoma based on the type of costs**

Mean costs	Type of treatment protocol		P
	IEV	ESHAP	
Medical direct costs	$1191.10 \pm 610.74$	$1819.57 \pm 789.73$	$< 0.001$
Non-medical direct costs	$237.06 \pm 207.42$	$208.39 \pm 179.7$	0.545
Indirect costs	$598.24 \pm 584.25$	$456.83 \pm 666.09$	0.249
Total	$2026.42 \pm 916.91$	$2484.79 \pm 1060.27$	0.123

The amounts are in United States dollar (USD).

IEV: Ifosfamide, epirubicin, and etoposide; ESHAP: Etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin

**Table 2. The cost components of Ifosfamide, epirubicin, and etoposide (IEV) and Etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin (ESHAP) regimens in lymphoma as included in the analysis**

Strategy	Costs components	Costs (USD)	The proportion to total costs (%)
ESHAP	Medical direct costs	69,143.72	73.0
	Chemotherapy drugs	32,943.08	35.0
	Hospitalization	9,931.37	11.0
	Sonography	775.13	1.0
	Radiology	2,751.31	3.0
	MRI	621.72	1.0
	Surgical	4,299.56	5.0
	Laboratory tests	8,800.97	9.0
	CT scan	2,955.19	3.0
	Visits	998.79	1.0
	Other	5,066.61	5.0
	Non-medical direct costs	7,918.85	8.0
	Traveling	3,980.62	4.0
	Lodging	2,111.43	2.0
	Phone	890.19	1.0
	Auxiliary equipment	68.63	< 0.1
	Special diet	867.99	1.0
	Indirect costs	17,359.71	18.0
	Time spent by the patient	13,362.94	14.0
	Time spent by the patient's accompany	3,996.77	4.0
	Total	94,422.29	
IEV	Medical direct costs	32,159.87	59.0
	Chemotherapy drugs	13,201.45	24.0
	Hospitalization	3,451.76	6.0
	Sonography	557.13	1.0
	Radiology	1,441.26	3.0
	MRI	282.60	1.0
	Surgical	4,339.93	8.0
	Laboratory tests	3,863.54	7.0
	CT scan	1,929.75	4.0
	Visits	609.61	1.0
	Other	2,482.84	5.0
	Non-medical direct costs	6,400.89	11.0
	Traveling	4,037.14	7.0
	Lodging	1,320.15	2.0
	Phone	680.26	1.0
	Auxiliary equipment	129.19	0.2
	Special diet	234.15	0.4
	Indirect costs	16,152.60	30.0
	Time spent by the patient	15,179.65	28.0
	Time spent by the patient's accompany	972.95	2.0
	Total	54,713.36	

IEV: Ifosfamide, epirubicin, and etoposide; ESHAP: Etoposide, solu-medrol-methylprednisolone, high-dose ara-C-cytarabine, and platinol-cisplatin; USD: United States dollar; MRI: Magnetic resonance imaging; CT: Computed tomography

## Discussion

This was the first cost-analysis in patients with lymphoma in Iran. Given that, cancer is one of

the major causes of death in Iran,<sup>13</sup> and lymphoma is among the ten most common cancers,<sup>14</sup> also, IEV and ESHAP drugs regimens are common drugs in the treatment of

lymphoma, we believe that evaluating the costs of these drugs regimens is very necessary.

Our results in this study indicated that the mean direct cost in ESHAP regimen ( $1191.1 \pm 610.74$  USD) was significantly more than IEV regimen ( $1819.57 \pm 789.73$  USD). In addition, the total cost of chemotherapy in ESHAP regimen was 32943.08 ( $866.92 \pm 354.91$ ) USD; it was 47.7% of medical direct costs. While in IEV regimen, the total cost of chemotherapy was 13201.45 ( $488.94 \pm 338.57$ ) USD, which was 41.04% of medical direct costs. These results could be due to high costs of chemotherapy in the ESHAP. Besides, more hospitalization would be created more paraclinical costs. Regarding the cost analysis, absolute comparisons to earlier studies cannot be made due to the different methodologies and great difference in costs between countries. Beard et al.,<sup>9</sup> Gruschkus et al.,<sup>15</sup> Kuderer et al.,<sup>16</sup> Lee et al.,<sup>17</sup> Norum et al.,<sup>18</sup> Ray et al.<sup>19</sup> and Sweetenham et al.,<sup>20</sup> concluded that the main cost drivers were medical direct costs, particularly chemotherapy. Moreover, earlier discharge of patients with lymphoma would reduce the hospitalization and consequently the medical direct costs.

However, the difference in the mean of non-medical direct costs and indirect costs in two regimens was not significant. The occupation and the absence from work determine the amount of indirect costs. These items do not follow the specific trend in the two groups. So, we can say more length of stay reduced income further by the more absence from work. Some of patients experienced more costs, including patients with higher travel costs, because of several stages of treatment and long courses. Overall, most of patient's income was spent on out-of-pocket costs for all expenditures incurred because of lymphoma. In the meantime, the ESHAP regimen was more expensive compared to the IEV regimen. So, insurance coverage should be considered in these patients to reduce the out of pocket.

Some limitations of our study must be discussed in evaluating the results. The small number of participants and short follow-up period can restrict the generalization of the findings to other setting. Assessment of a longer follow-up period is unlikely to alter our main findings, since there is no evidence to indicate that follow-up costs after discharge would reverse the results. Although our sample size was relatively small, it is the largest sample of patients with Hodgkin and non-Hodgkin lymphoma considered up until now in an out-of-pocket costs analysis.

Due to the difference in costs, generalizability to other hospitals may be limited. Nevertheless, therapeutic methods is similar between this hospital and others. Although, we cannot generalize these findings to other countries due to socialized medicine, worker's wages and drugs costs are dissimilar.

Particularly, chemotherapy costs are the highest costs in both regimens; but these are not covered by insurance, and patients pay these costs directly.

## Conclusion

Since patients with IEV regimen experienced a trend toward less neutropenia and, hence, had a trend toward fewer hospitalization days, the related cost was 3451.76 USD with savings of 6479.61 USD compared with the ESHAP regimen. Overall, most of patient's income was spent on out-of-pocket costs for all expenditures incurred because of lymphoma.

## Conflict of Interests

Authors have no conflict of interests.

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